APPLIED ORGANOMETALLIC CHEMISTRY
Appl. Organometal. Chem. 2002; **16**: 104–107

Materials, Nanomaterials and Synthesis AOC

New steroid-group-containing borazine compounds and their ^{13}C NMR spectra

Hiroshi Yamashita, Naoko Koda, Teiichi Murakami and Yuko Uchimaru*

National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba Central 5-2, Tsukuba, Ibaraki 305-8565, Japan

Received 6 June 2001; Accepted 17 October 2001

New borazine compounds containing steroid units (cholesteryl and stigmasteryl) were prepared by the reactions of *B,B′,B″*-trichloro-*N,N′,N″*-trimethylborazine with the 3-chloro derivatives of the corresponding steroids under Grignard conditions. The products were characterized by ^{13}C–^{1}H correlation NMR measurements to give fully assigned ^{13}C NMR data. Copyright © 2001 John Wiley & Sons, Ltd.

KEYWORDS: borazine; steroid; Grignard reaction; ^{13}C NMR

Boron-containing monomeric and polymeric compounds have not only been utilized as useful synthetic intermediates or catalysts in organic synthesis,[1,2] but they have also attracted increasing interest as new functional materials.[3–5] In this context we have prepared new boron polymers with six-membered borazine ring units comprising alternating boron and nitrogen atoms, and have examined their thermal properties.[6] In borazine chemistry, although some monomeric and polymeric compounds have been investigated to make boron nitride ceramics,[7] other applications have been few. Since borazine has three boron atoms in the ring, borazine compounds will conceivably become good candidates as neutron capture agents for destruction of cancer cells in boron neutron capture therapy (BNCT).[8] In connection with BNCT, many interesting boronic acid or boron cluster derivatives that contain units of cellular building blocks or metabolic compounds have been developed to improve effectiveness.[8] However, borazine derivatives containing cellular units have not been reported to date. Herein are reported the first examples of borazine derivatives with steroid units and the assignment of their ^{13}C NMR data.

EXPERIMENTAL

Solvents were dried with calcium hydride, and distilled under nitrogen before use. Cholesteryl chloride (**2a**) was purchased and used as received. Stigmasteryl chloride[9] (**2b**) was prepared by the reaction of stigmasterol with $SOCl_2$ (0 °C, 1 day) according to a literature method.[10] All reactions for the preparation of **1, 2b**, and **3a, b** were carried out under nitrogen.

*Correspondence to: Y. Uchimaru, National Institute of Advanced Science and Technology, Tsukuba Central 5-2, Tsukuba, Ibaraki 305-8565, Japan.
E-mail: y-uchimaru@aist.go.jp

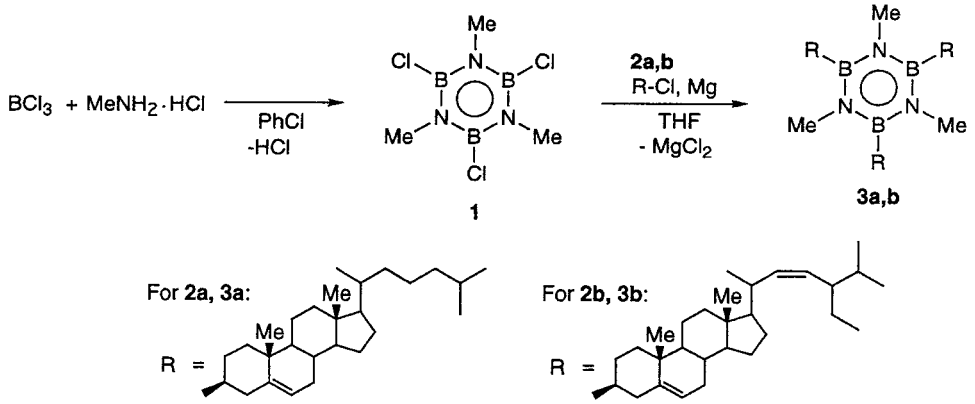
Synthesis of *B,B′,B″*-trichloro-*N,N′,N″*-trimethylborazine[11] (1)

To a suspended mixture of $MeNH_2{\cdot}HCl$ salt (0.16 mol) and chlorobenzene (100 ml) was added BCl_3 (0.25 mol) dropwise under gentle refluxing of chlorobenzene through a condenser cooled by dry-ice–ethanol over 3 h. The heating temperature was gradually increased to 160 °C over 4 h. The dry-ice condenser was removed and the solution was kept refluxing at 160 °C for 12 h to expel extra BCl_3 and any generated HCl completely. Evaporation of the solvent followed by sublimation of 50 °C (0.003 mmHg) gave pure **1** as a white solid in ≥90% yield.

Reaction of 1 with cholesteryl chloride (2a)

To a mixture of **1** (4.6 mmol), **2a** (13.9 mmol), and magnesium (34.0 mmol) was added tetrahydrofuran (THF) (15 ml). The resulting mixture was heated at 40 °C with stirring, and a small piece of I_2 was added. After the brown color had disappeared, the temperature was increased to 70 °C (30 min) and then to 80 °C (10 h). The reaction mixture was concentrated to give a white residue. Hexane was added (three times, 50 ml in total), and an insoluble solid was filtered off. Concentration of the hexane filtrate gave crude **3a**, which was purified by preparative gel permeation chromatography (GPC, toluene eluent) to give **3a** as a white solid in ≥80% yield.

DOI:10.1002/aoc.265



Scheme 1.

Reaction of 1 with stigmasteryl chloride (2b)

Under similar reaction conditions, **1** (2.0 mmol) was treated with **2b** (6.2 mmol) in the presence of magnesium (15.3 mmol). Concentration and hexane extraction gave crude **3b**, which was purified by preparative GPC to give **3b** as a white solid in ≥60% yield.

RESULTS AND DISCUSSION

B,*B*′,*B*″-Trichloro-*N*,*N*′,*N*″-trimethylborazine (**1**) was prepared from BCl_3 and $MeNH_2$·HCl by a slightly modified literature method[11] (Scheme 1). The key points of the reaction were the slow addition rate of BCl_3 (≥3 h addition

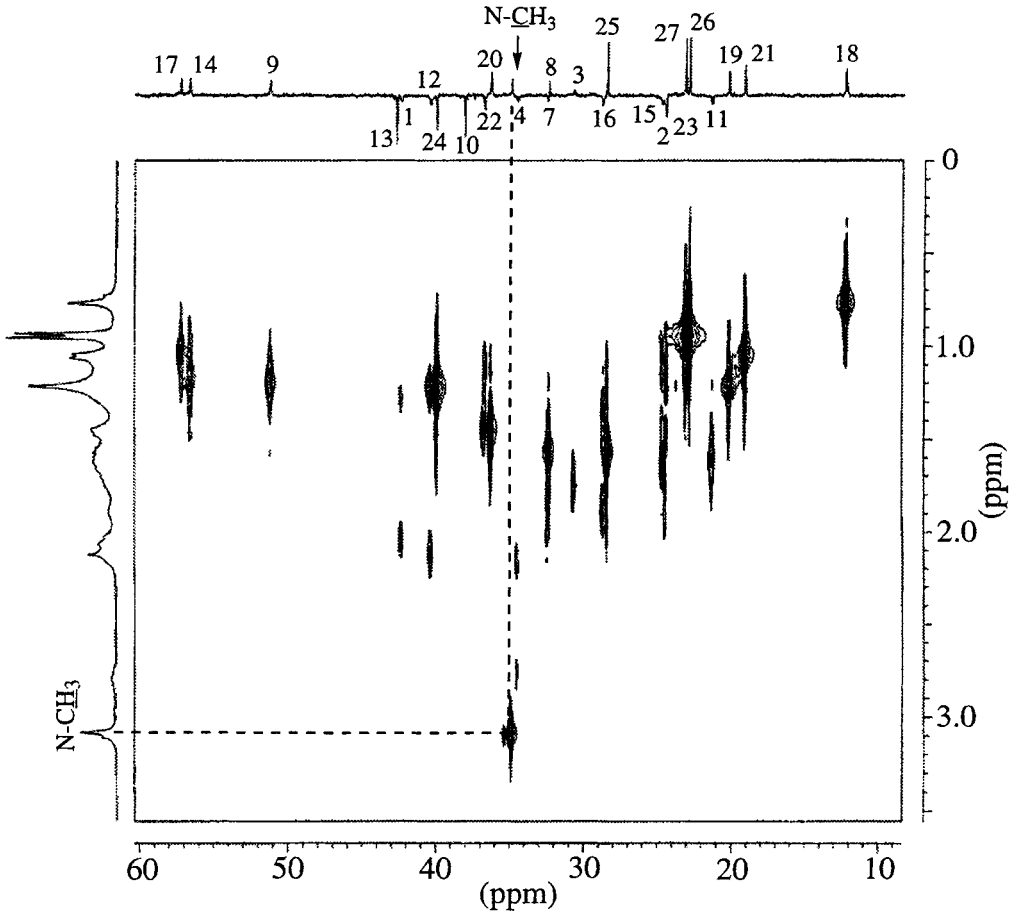


Figure 1. 2D NMR (^{13}C–^{1}H correlation) spectra of **3a** (in C_6D_6, partially expanded area). The ^{13}C NMR was measured by the GASPE technique, showing positive peaks for primary and tertiary carbon atoms and negative peaks for secondary and quaternary carbon atoms.

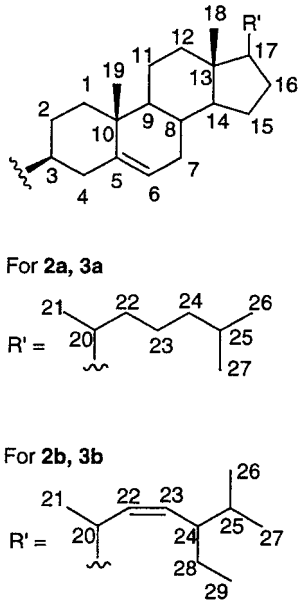


Figure 2. Atom labeling scheme for steroid units.

time for 0.25 mol scale reaction) and the use of an excess amount of BCl_3 (≥1.4 equiv.). The isolated yield was usually ≥90%. However, when the addition rate was too fast or the amount of BCl_3 was not enough the yield of **1** was significantly decreased, along with formation of unidentified byproducts that could not be separated in the subsequent sublimation procedure.

Introduction of a steroidal unit was achieved by treatment of **1** with a steroidal chloride **2** in the presence of magnesium (excess, ≥2 equiv. to **2**). Thus, when **1** was subjected to the reaction with cholesteryl chloride (**2a**, 3.0 equiv.) and magnesium (7.4 equiv.) in THF at 70 °C, a white solid of $MgCl_2$ was formed in 30 min. Further heating at 80 °C for 10 h followed by extraction with hexane gave a cholesteryl-group-substituted borazine **3a**. Oligomers of THF were also formed in the reaction, but they were not soluble in hexane, and could be easily removed by hexane extraction. In ^{1}H NMR of the concentrated reaction mixture, broad singlet-like peaks with almost equal intensity were observed at 1.35–1.45 ppm and 3.55–3.66 ppm, which seemed to be ascribable to the signals of THF oligomers (−O−C−CH_2− and −O−CH_2− moieties respectively). THF is known to undergo ring-opening polymerization under certain reaction conditions. Therefore, although the mechanism is not clear, the oligomeric compounds could be formed *via* ring-opening reaction of THF. The compounds were not soluble in hexane, and thus we could extract only the desired cholesterylborazine product by using hexane. The cholesterylborazine **3a** was purified by preparative GPC in ≥80% yield.

Borazine derivative **3a** was highly soluble in less polar organic solvents, such as hexane, toluene, benzene, etc. The structure was confirmed by ^{1}H and ^{13}C NMR spectra. The

Table 1. ^{13}C NMR chemical shifts (δ, ppm) of steroids **2** and **3**[a]

Carbon	2a	3a	2b	3b
N-CH_3	–	34.9	–	34.9
C-1	33.8	42.4	33.7	42.3
C-2	36.5	24.5	36.5	24.6
C-3	60.1	30.7	60.2	30.6
C-4	43.9	34.5	43.8	34.5
C-5	140.9	144.5	140.8	144.5
C-6	122.6	118.7	122.6	118.7
C-7	32.1	32.5	32.3	32.5
C-8	32.0	32.4	32.1	32.4
C-9	50.3	51.2	50.3	51.3
C-10	39.3	38.1	39.2	38.1
C-11	21.2	21.3	21.2	21.3
C-12	39.9	40.3	39.9	40.3
C-13	42.6	42.7	42.4	42.5
C-14	56.6	56.6	56.2	56.3
C-15	24.5	24.7	24.6	24.7
C-16	28.6	28.7	29.4	29.5
C-17	56.9	57.2	57.0	57.4
C-18	12.0	12.3	12.2	12.4
C-19	19.2	20.2	19.24	20.2
C-20	36.2	36.3	40.9	41.1
C-21	19.0	19.1	21.5	21.6
C-22	36.7	36.7	138.8	139.0
C-23	24.3	24.4	129.7	129.6
C-24	40.1	40.0	51.7	51.7
C-25	28.4	28.4	31.9	31.8
C-26	22.8	22.8	19.16	19.3
C-27	23.0	23.1	21.4	21.4
C-28	–	–	25.8	25.9
C-29	–	–	12.6	12.6

[a] In C_6D_6. For the numbering sequence, see Fig. 2.

assignment of each ^{13}C NMR signal was based on NMR measurements using GASPE[12] and ^{13}C–^{1}H correlation techniques (Fig. 1) and literature data for steroid derivatives.[10,13,14] The ^{13}C NMR chemical shifts of **3a** are summarized in Table 1, along with those of **2a**. The N−Me signals of **3a** were observed at 3.08 (^{1}H) and 34.9 ppm (^{13}C). The C-3 tertiary carbon signal appeared at 30.7 ppm. The signal was significantly broad and weak, probably due to partially relaxed scalar coupling $J(^{13}C^{11}B)$.[15] The order of the C-3 chemical shift is 71.3 (cholesterol) >60.1 (**2a**) >30.7 ppm (**3a**), presumably reflecting the electronegativities of the attached heteroatoms [χ_p = 3.5 (O) >3.0 (Cl) >2.0 (B)].

Likewise, a stigmasteryl unit could be introduced into the borazine ring by using stigmasteryl chloride **2b** in place of **2a** to give the corresponding borazine derivative **3b**. Based on the GASPE and ^{13}C–^{1}H correlation NMR measurements, and the literature data of stigmasterol,[14] all the ^{13}C NMR signals could be assigned consistently (Table 1). Similar trends for

the C-3 chemical shifts were also observed in the series of stigmasteryl derivatives: 71.7 (stigmasterol) >60.2 (**2b**) >30.6 ppm (**3b**). Compound **3b** has a reactive C═C bond in the steroid side chain, and by further modification it would be possible to add hydrophilic properties to the lipophilic compound.

To summarize, new borazine derivatives with steroid units were prepared and the ^{13}C NMR signals were fully assigned.

REFERENCES

1. Miyaura N and Suzuki A. *Chem. Rev.* 1995; **95**: 2457.
2. Vaultier M and Carboni B. In *Comprehensive Organometallic Chemistry II*, vol. 11, Abel EW, Stone FGA, Wilkinson G (eds). Pergamon: Oxford, 1995; chapter 5.
3. Matsumi N and Chujo Y. In *Contemporary Boron Chemistry*, Davidson M, Hughes AK, Marder TB, Wade K (eds). Royal Society of Chemistry: Cambridge, 2000; 51.
4. Keller TM and Son DY. In *Polymeric Materials Encyclopedia*, vol. 5, Salamone JC (ed). CRC: New York, 1996; 3262.
5. Peters EN. *J. Macromol. Sci. C Rev. Macromol. Chem.* 1979; **17**: 173.
6. Uchimaru Y, Koda N and Yamashita H. *Phosphorus Sulfur Silicon Relat. Elem.* 2002; in press.
7. Paine RT and Sneddon LG. *CHEMTECH* 1994; **24**(7): 29.
8. Soloway AH, Tjarks W, Barnum BA, Rong F-G, Barth RF, Codogni IM and Wilson JG. *Chem. Rev.* 1998; **98**: 1515.
9. Broome J, Brown BR and Summers GHR. *J. Chem. Soc.* 1957; 2071.
10. Buchanan HJ, Cox PJ, Doidge-Harrison SMSV, Howie RA, Jaspars M and Wardell JL. *J. Chem. Soc. Perkin Trans.* 1997; 3657.
11. Haworth DT. *Inorg. Synth.* 1972; **13**: 43.
12. Cookson DJ and Smith BE. *Org. Magn. Reson.* 1981; **16**: 111.
13. Blunt JW and Stothers JB. *Org. Magn. Reson.* 1977; **9**: 439.
14. Holland HL, Diakow PRP and Taylor GJ. *Can. J. Chem.* 1978; **56**: 3121.
15. Wrackmeyer B. *Z. Naturforsch. Teil B* 1982; **37**: 788.